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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
SITTON, JEHANNE SOUAYA	
ART UNIT	PAPER NUMBER
1634	

DATE MAILED: 07/26/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/655,543	SHATTUCK ET AL.	
	Examiner	Art Unit	
	Jehanne S. Sitton	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12 May 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-20* is/are pending in the application.

4a) Of the above claim(s) *7-9,12 and 15-20* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-6, 10-11, 13-14* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Currently, claims 1-20 are pending in the instant application. Claims 1-6, 10-11 and 13-14 are under examination at this time. Claims 7-9, 12, and 15-20 are withdrawn from consideration as being drawn to non elected inventions. The amendments and arguments have been thoroughly reviewed but are insufficient to place the instant application in condition for allowance. The following rejections are either newly applied as necessitated by amendment, or are maintained from the previous office action. They represent the complete set being presently applied to the instant application. Response to arguments follow. This action is FINAL.

2. The rejections under 35 USC 112, second paragraph made in the previous office action are withdrawn in view of the amendments to the claims.

Claim Objections

3. Claims 3 and 13 are objected to because of the following informalities: the claims contain a misspelling as they recite "TCB1D1" instead of "TBC1D1". Appropriate correction is required.

Specification

4. The amendment filed 5/12/2006 is objected to under 35 U.S.C. 132(a) because it introduces new matter into the disclosure. 35 U.S.C. 132(a) states that no amendment shall introduce new matter into the disclosure of the invention. The added material which is not supported by the original disclosure is as follows: Lines 7-9 of the first replacement paragraph at page 2 of the response and the last 3 lines of the 2nd replacement paragraph at page 2 of the

response. The subject matter which was newly added, is not supported by the original disclosure. It is suggested that applicant disable the hyperlink, for example, by reciting: "available on the world wide web at ncbi.nlm.nih.gov."

Applicant is required to cancel the new matter in the reply to this Office Action.

Claim Rejections - 35 USC § 112

5. Claims 3 and 13 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 3 and 13 are indefinite in the recitation of "first TBC1D1 coding exon (SEQ ID NO: 33)", because it is unclear if the recitation of SEQ ID NO: 33 inside the parenthesis is intended to be a limitation of the claim or not. It is not clear if the inclusion within the parenthesis is intended as an example, but not limiting the claim. It is suggested that the claim be amended to recite "first TBC1D1 coding exon, SEQ ID NO: 33, or the complement thereof".

Further, the recitation of "a cytidine to thymine transition at the 373rd nucleotide for the TBC1D1 coding sequence of an alternative transcript comprising the coding sequence encoded by the first TBC1D1 exon (SEQ ID NO: 33), or the complement thereof" is confusing in the recitation of "coding sequence encoded by the first... exon" as it is unclear if the recitation refers to a protein or nucleic acid. The term "encoded by" suggests a nucleic acid sequence, and therefore the recitation of "coding sequence encoded by" is unclear. The specification does not appear to provide for such recitation. Accordingly, the metes and bounds of the recitation are unclear.

6. Claims 1-6, 10-11, and 13-14 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The rejection is maintained for claims 1-2, 4-6, 10-11 and 14, but contains new grounds regarding the amendments to claims 3 and 13.

The claims are drawn to a method of determining whether a human subject is at risk for developing obesity wherein the detection of any polymorphism in any TBC1D1 encoding nucleic acid, or "a C to T transition at the 373rd nucleotide for the TBC1D1 coding sequence of an alternative transcript comprising the coding sequence encoded by the first TBC1D1 exon (SEQ ID NO: 33), or the complement thereof", or degenerate variants of the R125W alteration, indicates that the subject is at risk for developing obesity. Additionally, the claims are drawn to a method of predicting in a human subject, the likelihood of developing obesity by detecting "a C to T transition at the 373rd nucleotide for the TBC1D1 coding sequence of an alternative transcript comprising the coding sequence encoded by the first TBC1D1 exon (SEQ ID NO: 33), or the complement thereof". The claims are further limited to wherein the nucleotide variant is detected by determining the sequence of the TBC1D1 gene.

The claims are drawn to analysis using genomic sequences as well as mRNA or cDNA. The specification, however, does not teach the full sequence of the TBC1D1 gene. The specification teaches that TBC1D1 has a number of splice variants (figure 1), however different sequences are taught in the '817 and '074 provisional applications as well as in the prior and post

filing date art, from those disclosed in the instant specification. Accordingly, not only do the claims encompass sequences which were not known in the art or taught in the specification at the time of filing, but the designation of a specific nucleotide or amino acid is not clear based on the number of different sequences encompassed by the claims.

With regard to designations of nucleotide positions in any TBC1D1 encoding nucleic acid, Genbank Accession number NM_015173 teaches a version of an mRNA sequence with 5688 nucleotides as of September 2005 for TBC1D1. However, more than one version of the sequence exists, the first version dated October 2002 with only 2362 base pairs. With regard to genomic sequences, the specification teaches that the TBC1D1 consensus cDNA is covered by three human genomic sequences: Genbank Accession numbers AC021106, AC009595, and AC044902. However, sequences in Genbank can be changed (as exemplified above), such that the designation of a Genbank Accession number does not provide for a fixed sequence. In the instant case, 6 different versions of AC021106 exist from January 2000 to March 2002. It is not known which version is relied on by the specification. Not only do 3 different versions of AC009595 exist, from August 1999 to June 2000, but also the accession number has been replaced by AC108933, which contains 3 different versions from February 2002 to March 2002. 2 different versions of AC044902 exist (April to May of 2000) and it has also been replaced by AC098680, which contains 3 different versions from October 2001 to February 2002. It is not known which of any of these versions is relied on by the specification.

Further, all of the current claims encompass a large genus of nucleic acids which comprise polymorphisms in any TBC1D1 encoding nucleic acid sequence, which are not disclosed in the specification. The genus includes an enormous number of polymorphisms for

which no written description is provided in the specification. This large genus is represented in the specification by only the particularly named 3 polymorphisms for which data is provided demonstrating an association with the obesity. Thus, applicant has express possession of only 3 particular polymorphisms, in a genus which comprises hundreds of millions of different possibilities. Here, no common element or attributes of the sequences are disclosed which would permit selection of sequences as polymorphisms. No structural limitations or requirements which provide guidance on the identification of sequences which meet these functional limitations of associating a polymorphism with risk of developing obesity is provided. Further, these claims expressly encompass all the different possible allelic variants including insertions, deletion, substitutions and transversions at thousands of different sites. No written description of alleles, of upstream or downstream regions containing additional sequence, which are associated with any phenotype are described in the specification. Even in the narrower dependent claims, such as claim 3, the claims encompass any nucleotide variants resulting in a specific amino acid substitution, however only a specific nucleotide change has been taught in the specification. No predictable correlation between the structural alteration in the amino acid R125W variant and a risk for developing obesity is provided by the specification. At page 54, the specification teaches that R125 is conserved in mice and is in the phosphotyrosine interacting domain. However, the specification provides no evidence that any nucleotide change resulting in the R125W alteration at this position, in either mice or human sequences, provides a predictable association with risk for developing obesity. The specification teaches that this specific "C373T" polymorphism was found in 22 control chromosomes. Thus it is unclear whether the association between the presence of such polymorphism "C373T" and risk for developing obesity it due to linkage with

another disease causing or disease associated mutation or polymorphism, whether such "C373T" polymorphism in obese patients was due to it's presence in a larger disease associated haplotype which is absent in the control chromosomes, or if in fact, the change from Arg to Trp at position 125 is a mutation which alters the activity of TBC1D1 in some way and therefore increases the chances of a human subject developing obesity.

The specification provides no correlation between structure of polymorphisms and the function of such polymorphisms with an increased risk for obesity. The polymorphisms shown are not representative of the genus of any polymorphism associated with an increased risk for developing obesity because it is not clear which polymorphisms within "any" TBC1D1 encoding nucleic acid sequence would have the same affect. It is not clear whether the polymorphisms shown affect the function of TBC1D1 or whether they may simply represent markers for another gene that is in linkage disequilibrium with the specific alleles at issue, and the actual gene which is involved in an increased risk for obesity may be tens of thousands of nucleotides distant from the polymorphisms described in the specification. The specification does not teach the function of TBC1D1 nor how it's function, or lack of function, or altered function are predictably associated with obesity. Although the specification teaches that the R125W mutation is in the PID domain in mice, the specification does not teach how this domain or the specific mutation are involved with obesity. The specification is also silent with regard to any structure/function correlation with regard to the remaining 2 polymorphisms listed.

In analysis of the claims for compliance with the written description requirement of 35 U.S.C. 112, first paragraph, the written description guidelines note regarding genus/species situations that "Satisfactory disclosure of a ``representative number'' depends on whether one of

skill in the art would recognize that the applicant was in possession of the necessary common attributes or features of the elements possessed by the members of the genus in view of the species disclosed." (See: Federal Register: December 21, 1999 (Volume 64, Number 244), revised guidelines for written description.) In the instant case, the specification fails to teach the necessary common attributes or features of the genus of encompassed nucleic acids and polymorphisms in view of the species disclosed. As such, one of skill in the art would not recognize that applicant was in possession of the genus of nucleic acids and polymorphisms encompassed by the broadly claimed invention.

Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the 'written description' inquiry, whatever is now claimed." (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116.)

The skilled artisan cannot envision the detailed chemical structure of the encompassed nucleic acids and polymorphisms, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it. The nucleic acid itself is required. See Fiers v. Revel, 25 USPQ2d 1601, 1606 (CAFC 1993), and Amgen Inc. V. Chugai Pharmaceutical Co. Ltd., 18 USPQ2d 1016. The current situation is a definition of the compound solely based on its functional utility, as a polymorphism, without any definition of the particular polymorphisms claimed.

Finally, University of California v. Eli Lilly and Co., 43 USPQ2d 1398, 1404, 1405 held that:

To fulfill the written description requirement, a patent specification must describe an invention and do so in sufficient detail that one skilled in the art can clearly conclude that "the inventor invented the claimed invention." Lockwood v. American Airlines, Inc., 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (1997); In re Gosteli, 872 F.2d 1008, 1012, 10 USPQ2d 1614, 1618 (Fed. Cir. 1989) (" [T]he description must clearly allow persons of ordinary skill in the art to recognize that [the inventor] invented what is claimed."). Thus, an applicant complies with the written description requirement "by describing the invention, with all its claimed limitations, not that which makes it obvious," and by using "such descriptive means as words, structures, figures, diagrams, formulas, etc., that set forth the claimed invention." Lockwood, 107 F.3d at 1572, 41 USPQ2d at 1966.

An adequate written description of a DNA, such as the cDNA of the recombinant plasmids and microorganisms of the '525 patent, "requires a precise definition, such as by structure, formula, chemical name, or physical properties," not a mere wish or plan for obtaining the claimed chemical invention. Fiers v. Revel, 984 F.2d 1164, 1171, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993). Accordingly, "an adequate written description of a DNA requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it; what is required is a description of the DNA itself." Id. at 1170, 25 USPQ2d at 1606.

Additionally, the claims (3 and 13) have been amended to recite "a cytidine to thymidine transition at the 373rd nucleotide of the TBC1D1 coding sequence of an alternative transcript comprising the coding sequence encoded by the first TBC1D1 coding exon (SEQ ID NO: 33), or the complement thereof". The response has not provided any reference to the specification to provide support for this amended recitation. The specification as well as the response have been thoroughly reviewed. However, the specification does not appear to support "the 373rd nucleotide of the TBC1D1 coding sequence of an alternative transcript comprising the coding sequence encoded by the first TBC1D1 coding exon (SEQ ID NO: 33)". Accordingly, the amendment appears to enter new matter into the claimed invention.

Response to Arguments

7. The response traverses the rejection. The response refers to Exhibit A as evidence that the specification teaches the full sequence of the TBC1D1 gene. The response suggests that the

basis for the rejection is based on an incomplete understanding of the specification and accompanying sequence listing, and provides pages 17-19 in the response as explanation. This argument, as well as the response, have been thoroughly reviewed but were not found persuasive to overcome the rejection. Exhibit A is directed to an informal sequence listing which states "genomic sequence" and which does not appear to be part of the specification. Neither it, nor the specification, provide the skilled artisan with guidance as to the full organization of the TBC1D1 gene. In detecting an alteration in a TBC1D1 encoding nucleic acid molecule, which encompasses the TBC1D1 gene, the skilled artisan would need to know the boundaries of relevant portions of the gene, such as the promoter, enhancers, complete 5' and 3' UTR's, introns, etc. The disclosure in the informal sequence listing does not provide the skilled artisan with such guidance so that the skilled artisan would be capable of determining which aspects of SEQ ID NO: 28, met the limitations of the claims, or if SEQ ID NO: 28 comprised the entire gene sequence including promoters, enhancers, complete 5' and 3' UTRs, etc. With regard to item 15 at page 19 of the response, it is not clear if the promoters (regarding exons 22 and 23) are taught within SEQ ID NO: 28, or where the "important regulatory elements" which impart tissue and/or temporal specificity are located.

At page 19, last para, the response appears to argue that the claims are not directed to compositions of matter but instead to methods of assessing increased risk of human subjects developing obesity "based upon a heretofore unknown association of mutations in the TBC1D1 gene with this risk". The response notes that the specification has provided examples of at least 3 nucleotide variants that appear to be associated with an increased risk for obesity in human subjects. The response further asserts that based on the disclosure in the specification, one of

average skill would appreciate that the inventors had discovered a much broader association between an increased risk for obesity and specific mutations in TBC1D1 and that such skilled artisans would immediately appreciate that the inventors were in possession of at least three species which are sufficient support for a genus of methods directed to diagnosing an increased risk of obesity in human subjects by identifying polymorphisms within TBC1D1 nucleic acids. The response further asserts that the inventors are not required to set forth how or why their invention works and that the Written Description requirement is met by the disclosure of a single working embodiment of the invention, citing the Written Description guidelines (see page 21 of the response).

These arguments have been thoroughly reviewed but were not found persuasive. The response correctly notes, and the office action does not question the fact that the specification teaches possession of 3 nucleotide alterations which appear to be associated with obesity. However, in the instant case, the claims are broadly drawn to methods that encompass that ANY polymorphism, alteration, or mutation in TBC1D1 or any degenerate variant encoding R125W would be similarly diagnostic. It is not the presence of the 3 specific alterations, but the absence of any structure function relationship and the absence of a representative number of species which supports the conclusion that there is insufficient descriptive support for the current claims. Firstly, the mutations shown are not representative of the genus of any alteration associated with an increased risk for obesity. Secondly, the claims are defined entirely by function, and there is no structure function relationship between undisclosed alterations in TBC1D1 nucleic acids and obesity risk. The written description guidelines note regarding genus/species situations that "Satisfactory disclosure of a ``representative number" depends on whether one of skill in the art

would recognize that the applicant was in possession of the necessary common attributes or features of the elements possessed by the members of the genus in view of the species disclosed." (See: Federal Register: December 21, 1999 (Volume 64, Number 244), revised guidelines for written description.) In the instant case, the specification fails to teach the necessary common attributes or features of the genus of encompassed nucleic acids and polymorphisms, alterations, mutations, etc in view of the species disclosed. As such, one of skill in the art would not recognize that applicant was in possession of the genus of nucleic acids and alterations encompassed by the broadly claimed invention. The specification has provided no correlation between the structure of the disclosed nucleotide alterations and how they function to provide increased risk for obesity.

In the instant case, the association of the identified 3 nucleotide variants with an increased risk of obesity could be due to a number of factors. For example, the specific nucleotide alterations could be linked in a disease associated haplotype, and while not being functionally responsible for the association (that is, not affecting the function of the encoded protein), they may be linked to alterations that are. Accordingly, degenerate variants encoding the R125W mutation may not even exist, or be in linkage disequilibrium with other causative alleles. Alternatively, or in addition, they may alter the function of TBC1D1 in some way so as to provide for an increased risk with obesity. The specification provides no guidance regarding either of these possibilities. The specification does not teach the function of TBC1D1 nor how it's function, or lack of function, or altered function are predictably associated with obesity. Although the specification teaches that the R125 is in the PID domain in mice, the specification does not teach how this domain or the specific R125W mutation affect the function of TBC1D1

to provide for increased risk of obesity. The specification is also silent with regard to any structure/function correlation with regard to the remaining 2 alterations disclosed. The examiner notes applicants vigorous objection to the "apparent requirement by the Examiner that the specification teach the molecular details of how mutations affect TBC1D1 function..." and the assertion in the response that it is well established law that an Applicant need not know how, nor describe the details of how their invention works (response page 21). This argument has been thoroughly reviewed but was not found persuasive. The claims are not limited to diagnosing an increased risk for obesity in a human subject comprising detecting the specific "C373T" alteration in SEQ ID NO: 1 and the examiner notes that a claim limited to such would not be rejected under the Written Description requirement of 35 USC 112, first paragraph. However, the claims are not limited to this alteration. Failure to provide a structure function correlation between the 3 alterations in TBC1D1 coding sequence recited in the specification and an increased risk for obesity is evidence that the specification does not set forth the necessary common attributes or features of the elements possessed by the members of the genus in view of the species disclosed. This issue fundamentally addresses whether there is any structure which the specification demonstrates is necessarily correlated with the function of increased risk for obesity. In this case, the answer is no. The genus encompassed by the claims includes an enormous number of possible polymorphisms and mutations which may be linked to an undisclosed haplotype, and/or alter the function of TBC1D1 in some way to provide for an increased risk for obesity. However, the specification provides no description or guidance to the skilled artisan to identify other alterations within the TBC1D1 gene, or cDNA's encoding different splice variants, which would be associated with disease.

At page 21, the response argues that the Written Description requirement is met by the disclosure of a single working embodiment of the invention. This argument has been thoroughly reviewed but was not found persuasive. As noted in the MPEP 2163 (II)(A) (3aii) "For each claim drawn to a genus: "A "representative number of species" means that the species which are adequately described are representative of the entire genus. Thus, when there is substantial variation within the genus, one must describe a sufficient variety of species to reflect the variation within the genus. >The disclosure of only one species encompassed within a genus adequately describes a claim directed to that genus only if the disclosure "indicates that the patentee has invented species sufficient to constitute the gen[us]." See *Enzo Biochem*, 323 F.3d at 966, 63 USPQ2d at 1615; *Noelle v. Lederman*, 355 F.3d 1343, 1350, 69 USPQ2d 1508, 1514 (Fed. Cir. 2004) (Fed. Cir. 2004)("[A] patentee of a biotechnological invention cannot necessarily claim a genus after only describing a limited number of species because there may be unpredictability in the results obtained from species other than those specifically enumerated.").". In the instant case, for the reasons noted above, the 3 alterations disclosed are not representative of the entire genus claimed because there is substantial variation in the genus encompassing millions of different alterations whose effects are not predictable, nor are they predictable based on the reference to only 3 alterations in view of the lack of any guidance as to how those mutations affect TBC1D1 nucleic acids or proteins to provide for an increased risk of obesity.

At pages 22-24, the response cites *Invitrogen Corporation v. Clonetech Laboratories Inc.*, 429 F. 3d 1052 (Fed. Cir. 2005) and argues that the application clearly provides sufficient written description of the claimed invention because it recites three representative embodiments

of the claimed methods diagnosing an increased risk of obesity in human subjects. This argument has been thoroughly reviewed but was found unpersuasive. Regarding *Invitrogen,* The United States District Court for the District of Maryland ruled that the claims were not invalid for lack of Written Description and that there had been established a sufficiently known correlation between RNase H activity in RT (function) and the RT gene made by a deletion mutation to satisfy the PTO test for written description. In the patent at issue, there had been disclosed in the prior art and references disclosed in the specification for sequences of RT genes from other species. Further, there was a known correlation between the RNase H activity in RT and the RT deletion mutant and "members of the RT gene family shared significant homologies from one species of RT to another". In contrast, in the instant case, there is no disclosed or known correlation between the 3 nucleotide alterations in TBC1D1 (structure) and the effect of the disclosed alterations on TBC1D1 nucleic acids or proteins in obesity risk (function). The specification only provides analysis in different risk groups and teaches that particular alterations in nucleotide sequences were found. There is no structure in common between the specific alterations taught in the specification and any other alterations in a TBC1D1 encoding sequence that may exist.

At page 24, the response asserts that reference to *Amgen v. Chugai* is misplaced because the present invention is not drawn to nucleic acids, but rather to a diagnostic method based upon identifying nucleotide variations within them. This argument has been thoroughly reviewed but was not found persuasive. The instant claims are directed to diagnosing an increased risk for obesity by detecting any alteration in any TBC1D1 encoding nucleic acid. They are not simply a method for detecting nucleotide variations but rather to detecting obesity associated alterations.

For the reasons noted above, the instant claims are directed to a genus of possible mutations for which the 3 species asserted in the response are not representative. For these reasons and the reasons already made of record, the rejection is maintained.

8. Claims 1-6, 10-11 and 13-14 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for determining whether a human subject is at risk for developing obesity comprising obtaining a sample form the human subject comprising a TBC1D1 coding sequence and detecting a nucleotide variant selected from the group consisting of a) a C to T transition at nucleotide 466 of SEQ ID NO: 33, b) a C to T transition at nucleotide 373 of SEQ ID NO: 1, and c) the complement of a or b, and diagnosing the human subject as being at risk for developing obesity or a method for predicting in a human subject, the likelihood of developing obesity comprising detecting the presence of a nucleotide variant selected from the group consisting of a) a C to T transition at nucleotide 466 in SEQ ID NO: 33, b) a C to T transition at nucleotide 373 of SEQ ID NO: 1, and c) the complement of a or b, wherein the presence of said nucleotide variant predicts that said subject has an increased likelihood of developing obesity, does not reasonably provide enablement for a method for determining or predicting whether a human subject is at risk for developing obesity by detecting any nucleotide variant in any TBC1D1 encoding nucleic acid, or a C to T transition at the 373rd nucleotide for the TBC1D1 coding sequence of an alternative transcript comprising the coding sequence encoded by the first TBC1D1 exon (SEQ ID NO: 33), or the complement thereof, or for detecting any nucleotide variant which results in an arginine to tryptophan substitution at the 125 amino acid of a TBC1D1 protein, or the complement thereof. The specification does not

enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims. There are many factors to be considered when determining whether there is sufficient evidence to support determination that a disclosure does not satisfy the enablement requirements and whether any necessary experimentation is undue. These factors have been described by the court in *In re Wands*, 8 USPQ2d 1400 (CA FC 1988). *Wands* states at page 1404,

> "Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

The amended claims are drawn to a method of determining whether a human subject is at risk for developing obesity wherein the detection of any polymorphism in any TBC1D1 encoding nucleic acid, or "a C to T transition at the 373rd nucleotide for the TBC1D1 coding sequence of an alternative transcript comprising the coding sequence encoded by the first TBC1D1 exon (SEQ ID NO: 33), or the complement thereof", or degenerate variants of the R125W alteration, indicates that the subject is at risk for developing obesity. Additionally, the claims are drawn to a method of predicting in a human subject, the likelihood of developing obesity by detecting "a C to T transition at the 373rd nucleotide for the TBC1D1 coding sequence of an alternative transcript comprising the coding sequence encoded by the first TBC1D1 exon (SEQ ID NO: 33), or the complement thereof". The claims are further limited to wherein the nucleotide variant is detected by determining the sequence of the TBC1D1 gene. The claims are further drawn to analysis using genomic sequences as well as mRNA or cDNA.

The nature of the claimed invention, therefore, requires the knowledge of predictive associations between any polymorphism in any TBC1D1 encoding nucleic acid or degenerate variants of the R125W mutation, and a human subjects risk for developing obesity.

The specification teaches (pages 53-54) that TBC1D1 is the founding member of a family of proteins with homology to tre-2/UPS6,BUB2, and cdc16 and contains a TBC box motif. The specification teaches that in mice, TBC1 showed differential expression in two mast cell lines. However, the specification does not teach the function or role of TBC1D1 in obesity and does not teach how it's function, an alteration in function, or absence of function, is associated with obesity. The specification asserts that the diagnostic/prognostic methods include determining the presence or absence of a substitution, deletion, insertion, or truncation in the PID or TBC domain of TBC1D1. However, the specification provides no predictable correlation that the presence or absence of "any" mutation in either of these two domains is associated with obesity. Although the specification asserts that Arg125, Lys119, Ser112, and Ser28 (relative to SEQ ID NO: 2) can be critical to the PID domain's optimal interaction with phosphotyrosine, the specification does not teach what role, if any, these amino acids or domains have with regard to obesity. Additionally, it is not clear that all such amino acids would be found in the large number of different TBC1D1 splice variants.

The specification teaches the identification of 3 nucleotide polymorphisms, "C373T," "T683G" and "C1174G", in obesity linked families (page 54), however, the specification provides no predictable association that broadly "any" alteration, in "any" TBC1D1 encoding nucleic acid is associated with increased risk for developing obesity. There are no common element or attributes of the sequences are disclosed which would permit selection of sequences

as polymorphisms. No structural limitations or requirements which provide guidance on the identification of sequences which meet these functional limitations of associating a polymorphism with risk of developing obesity is provided. Further, these claims expressly encompass all the different possible allelic variants including insertions, deletion, substitutions and transversions at thousands of different sites. No written description of alleles, of upstream or downstream regions containing additional sequence, which are associated with any phenotype are described in the specification. Even in the narrower dependent claims, such as claim 3, the claims encompass any nucleotide variants resulting in a specific amino acid substitution, however only a specific nucleotide change has been taught in the specification. No predictable correlation between the structural alteration in the amino acid R125W variant and a risk for developing obesity is provided by the specification. At page 54, the specification teaches that R125 is conserved in mice and is in the phosphotyrosine interacting domain. However, the specification provides no evidence that any nucleotide change resulting in the R125W alteration at this position, in either mice or human sequences, provides a predictable association with risk for developing obesity. The specification teaches that this specific "C373T" polymorphism was found in 22 control chromosomes. Thus it is not predictable whether the association between the presence of such polymorphism "C373T" and risk for developing obesity it due to linkage with another disease causing or disease associated mutation or polymorphism, whether such "C373T" polymorphism in obese patients was due to it's presence in a larger disease associated haplotype which is absent in the control chromosomes, or if in fact, the change from Arg to Trp at position 125 is a mutation which alters the activity of TBC1D1 in some way and therefore increases the chances of a human subject developing obesity.

The polymorphisms shown are not representative of the genus of any polymorphism associated with an increased risk for developing obesity because it is not clear which polymorphisms within "any" TBC1D1 encoding nucleic acid sequence would have the same affect. It is not clear whether the polymorphisms shown affect the function of TBC1D1 or whether they may simply represent markers for another gene that is in linkage disequilibrium with the specific alleles at issue, and the actual gene which is involved in an increased risk for obesity may be tens of thousands of nucleotides distant from the polymorphisms described in the specification. The specification does not teach the function of TBC1D1 nor how it's function, or lack of function, or altered function are predictably associated with obesity. Although the specification teaches that the detected R125W mutation is in the PID domain in mice, the specification does not teach how this domain or the specific mutation are involved with obesity. The specification is also silent with regard to any structure/function correlation with regard to the remaining 2 polymorphisms listed.

The art does not teach the function of the TBC1D1 protein splice variants, how they are involved in obesity, or how alterations in such are associated with obesity.

The quantity of experimentation in this area is extremely large as it requires analysis of each position in any TBC1D1 encoding sequence to determine whether any alteration at each position is associated with increased risk for developing obesity. As neither the art nor the specification provide guidance as to which alterations at positions throughout TBC1D1 are associated with an increased risk for developing obesity, or which positions throughout TBC1D1 are critical to the function of TBC1D1 in relation to obesity, such analysis is replete with trial and error experimentation, with the outcome of each analysis being unpredictable. Screening

each possible alteration in TBC1D1 represents an inventive and unpredictable undertaking in itself, with each of the many intervening steps, not providing any guarantee of success.

Thus, given the broad claims in an art whose nature is identified as unpredictable, the state of the prior art, the lack of guidance in the specification, the breadth of the claims and the quantity of experimentation necessary to practice the claimed invention, it would require undue experimentation to practice the invention commensurate in scope with the claims.

Response to Arguments

9. The response traverses the rejection. Firstly, it is noted that the response asserts that the rejection is partly based on "the state of the prior art provides little guidance". However, as noted in the previous office action and reiterated above, "the art does not teach the function of the TBC1D1 protein splice variants, how they are involved in obesity, or how alterations in such are associated with obesity". The art provides no guidance as to enablement of the claimed invention.

At pages 25-27, the response cites *Invitrogen Corporation v. Clonetech Laboratories Inc.*, 429 F. 3d 1052 (Fed. Cir. 2005) and Nat'l Recovery, 166 F.3d at 1196 (Fed. Cir. 1999) to support the enablement of the claimed invention. The response asserts that as in *Invitrogen*, the amended claims are enabled by the specification because the specification fully describes an operable embodiment, that is the C373T mutation in SEQ ID NO: 1, as well as T683G and C1174G variants. This argument has been thoroughly reviewed but was not found persuasive to overcome the rejection. As noted by the response regarding Nat'l Recovery, "the scope of enablement, in turn, is that which is disclosed in the specification plus the scope of what would

be known to one of ordinary skill in the art without undue experimentation". The instant claims are directed to methods of diagnosing or predicting an increased risk of obesity by detecting any alteration in any TBC1D1 nucleic acid or any R125W degenerate variant. However, the specification has provided no universal correlation between the mere presence of an alteration in TBC1D1 nucleic acids and risk of obesity. Further, the specification provides no assay, other than by actually screening individuals for obesity linked alterations, to identify disease associated alterations. The specification provides no correlation between the structure of the 3 alterations disclosed in the specification and how they affect TBC1D1 nucleic acids or proteins to provide for obesity risk. For example, the nucleotide variants set forth in the specification may be part of a larger "obesity risk" haplotype, or linked to causative mutations hundreds or thousands of nucleotides away. Accordingly, degenerate variants of the R125W mutants may not even exist, or be linked to such a haplotype. Alternatively, the disclosed 3 nucleotide variants may affect the function of TBC1D1 nucleic acids or the encoded protein, however neither the specification nor the art teach the function of TBC1D1 or how it's function, lack of function, or altered function provide for obesity risk. Accordingly, the specification provides no way to determine which, if any, additional alterations within TBC1D1 nucleic acids provide for risk of obesity other than by trial and error testing of a large number of patients and controls to determine if a predictable correlation exists between the mere presence of a nucleotide alteration in a TBC1D1 nucleic acid and obesity risk. The trial and error analysis required to enable the claimed invention is replete with unpredictable experimentation, and is not routine. There is no guarantee or likelihood of success that any other variants exist, nor any way to predict where they might be. Accordingly, the rejection is maintained.

Conclusion

10. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

11. No claims are allowed.

12. Any inquiry concerning this communication or earlier communications from the examiner should be directed to examiner Jehanne Sitton whose telephone number is (571) 272-0752. The examiner can normally be reached Monday-Thursday from 8:00 AM to 5:00 PM and on alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla, can be reached on (571) 272-0735. The fax phone number for this Group is (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

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For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

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7/24/06